Towards a cure: The fight against Zika virus

By Alaa Abdine

Despite the discovery of Zika virus more than a half-century ago, it wasn’t until 2015 that its threat became visible and the virus largely known. This was due to the Brazilian government revealing an association of viral infection with neurological disorders, including microencephaly in newborns. First discovered in the Zika forest in Uganda, the virus has traveled across the equatorial regions of Africa, moved to South Asia, and was later found in several Pacific Islands in the early 2000s. Zika is a single-stranded RNA virus of the Flaviviridae family, and it is related to dengue, yellow fever, and West Nile viruses. Early reports of Zika virus described the infection as “mild” since the first patient didn’t experience crippling pain which is associated with other similar diseases like dengue or chikungunya. It wasn’t until the late 2000s that researchers found that the infection can be transmitted sexually, and can be severe neurologically and autoimmune complications during pregnancy. Zika virus has now found its way to mainland USA, and the first locally-spread cases of Zika are hitting Miami. Since the Center for Disease Control (CDC) has already spent $194 million of the $222 million allocated by Congress to fight Zika, everyone is waiting for a bipartisan deal to address the potential crisis by unblocking a $1.1 billion legislative package to help fight the virus. Meanwhile, small but considerable efforts are being made to understand and contain the virus in the USA and around the world.

At the Icahn School of Medicine at Mount Sinai (ISMMS), the efforts are palpable as researchers are trying to identify the molecular interactions behind Zika infections, and discover druggable targets in order to come up with a solution to the outbreak. Recently, in May 2016, a collaborative effort between labs in the Department of Microbiology at Sinai, the Laboratory of Virology at the NIAID, and the Laboratory of Arbovirus and Imported Viral Diseases at the National Center of Microbiology in Madrid, Spain resulted in researchers identifying a viral protein, NS5, as a potential target for vaccines against Zika. The study, published in the journal Cell Host & Microbe, showed that producing viruses with an altered or deleted NS5 can trigger the immune system to produce interferon to fight the virus (1). Another Sinai effort came from the publication of the structure of the Zika RNA helicase, NS3. The protein is composed of three domains, and one of these domains interacts closely with NS5. The structural determination of NS3 has allowed researchers to identify some “druggable hotspots” in the protein, as targeting the RNA helicase may affect the virus’s ability to replicate (2). Finally, in a joint effort of 15 laboratories (from the NIH, NCATS, JHU, ISMMS, and others) using a drug repurposing screen, researchers have identified several compounds that potentially can be used to inhibit the replication of the virus and reduce embryonic neuronal damage (3). One of the compounds, emricasan, is a caspase inhibitor that has been studied in over 650 subjects (over sixteen clinical trials) across a broad range of liver disease etiologies and stages of progression. The drug is currently in phase 2 clinical trials, where it has shown no adverse events in human trials. It is still unknown whether it is safe to be used during pregnancy after a Zika infection has occurred in order to avoid congenital complications. In the same study, the combination of niclosamide, a drug used to treat worm infections, and PHA-690509, a CDK inhibitor, was shown to inhibit viral infection and reduce neuronal death by affecting virus replication. Unfortunately, pre-clinical studies and toxicology trials need to be done before these drugs can be used during pregnancy. Nonetheless, the use of niclosamide and CDK inhibitors may be helpful for non-pregnant patients facing non-congenital effects of the virus.

Together, these efforts will allow the scientific community to better understand the mechanisms by which Zika virus is infecting patients and causing neuronal damage in utero. These findings could be used in the fight against infections by other arboviruses, such as dengue, chikungunya, and West Nile virus, many of which can cause devastating illnesses in tropical regions and are becoming more frequent in countries where climbing temperatures and rising poverty rates are creating ideal environments for tropical mosquito-borne diseases.

References:

(1) Zika Virus Targets Human STAT2 to Inhibit Type I Interferon Signaling. A. Grant et al. Cell Host & Microbe. Volume 19, Issue 6, p882–890, 8 June 2016
(3) Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. M. Xu et al. Nature Medicine. Published online 29 August 2016.
With their stunning array of flowers, eucalyptus trees are a symbol of Australia and, of the 700 plus species, only 15 are found outside of Australia. Eucalypts play a vital role in Australia’s natural environment and are found abundantly throughout the country; the only major environment they do not inhabit is Australia’s rainforests. Interestingly, they release biochemicals which influence the growth, reproduction, and survival of other organisms - thus inhibiting the growth of other nearby plant species (this is called allelopathy). Every summer, Australia is burdened with large and devastating bushfires due to vast areas of eucalyptus forest. These trees constantly drop dry leaves and bark peelings onto the floor around them and together with the eucalyptus oil within can quickly turn a small fire into a fast-moving and raging inferno. As devastating as these fires are for the animals and people living nearby, the trees are adapted to be successful survivors. The release of seeds from gumnuts (seed pods) are actually triggered by fire, as they fall onto the nutrient-rich, ash-covered ground - free from competing plants and damaging insects. They will then quickly repopulate the forests and continue to be the dominating species of the Aussie bush.

In the 1850s during the Californian Gold Rush, Australians introduced the Tasmanian blue gum eucalyptus to California as an ornamental tree, but their use as a fast-growing supply of timber and eucalyptus oil was quickly exploited. Due to this fact, eucalyptus trees now populate large areas of California and are involved in most California wildfires. So it seems to me that you can’t grow the Aussie bush without catching Aussie bushfires.

Greetings fellow postdocs, The Postdoc Executive Committee (PEC) would like to thank the ISMMS postdoc community for participating in the 7th Annual Postdoc Symposium on Friday, September 23. The event was a huge success, with a record 275 attendees, 12 speakers and panelists, and over 30 guests at the networking reception representing over 15 companies and organizations. This annual event is organized by the PEC and the Office of Postdoctoral Affairs, and we are pleased it was such a huge success! The presentations and panel discussion were recorded and will be available on the ISMMS Postdoc website once they are ready, so if you missed the Postdoc Symposium you can still watch the terrific presentations from the day. Lastly, a follow-up survey on the Postdoc Symposium will soon be sent out so please fill it out - we use your feedback to improve upcoming symposiums and select next year’s theme!

On another note, I would like to bid a fond farewell to Dr. Alison Sanders, whose term as co-chair has come to an end. It have had the pleasure of working with Alison for the past 6 months - her passion and drive to improve the postdoc experience at ISMMS has been a motivating force and has led to the successful establishment of the 5-year postdoc term, mistreatment resource panel, and $50K salary minimum, just to name a few. As the principal investigator on a Burroughs Wellcome Fund grant, Alison spearheaded the first teacher training program at ISMMS (Future Leaders in Science Education and Communication Training program), creating much-needed professional development opportunities for postdocs at ISMMS. Even as her tenure as co-chair comes to an end, she will still be helping implement the inaugural Future Leaders in Project Management short course (applications now being accepted!). I am excited to move forward and serve my last 6 months as co-chair with Dr. Geneviève Galarneau, continuing the momentum Alison and I have built. Keep an eye out for continued progress in the upcoming year including a postdoc alumni career survey, more NYC-wide social events, and an updated postdoc handbook with clarified policies and resources, among many others.

Cheers,
Delaine

Delaine K. Ceholski and Alison P. Sanders are your PEC co-chairs

Ways to keep in touch

• Our website: http://icahn.mssm.edu/education/postdoctoral-training
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The Mount Sinai Postdoc Periodical
The zebrafish as an ideal model for human disease
By Elena Sanchez-Rodriguez

Most people think of zebrafish as little more than an easy household pet, as they are small and easy to care for. When it comes to animal research models, mice, rats, and fruit flies are the traditional choices. However, over the last few decades the use of zebrafish (Danio rerio) is steadily increasing in biomedical research. Why would a scientist choose to use a zebrafish to study human disease?

Even though zebrafish live their lives in water, they are not all that dissimilar from people. Zebrafish have all the major organs that humans do, with the exception of lungs and different reproductive organs. Many of the genes and critical pathways that are required to grow these features are highly conserved between humans and zebrafish. In fact, zebrafish share about 70% genetic identity with humans. In addition, as vertebrates, zebrafish are more closely related to humans than fruit flies or worms. So why use zebrafish when you could use mice? While mice are evolutionarily more similar to humans because they are mammals, zebrafish have several advantages over their furry competitors. One important advantage is that the adults are small and prefer to be housed in large groups. As a result, they require much less space and are cheaper to maintain than mice. Another advantage is that adult zebrafish breed rapidly (~every 10 days) and can produce as many as 50 to 300 eggs at a time.

Zebrafish embryos are laid and fertilized externally, which allows them to be easily manipulated in a variety of ways. The one-cell stage fertilized eggs can easily be injected with DNA, RNA or CRISPR/Cas9 to permanently edit their genes in order to generate transgenic or knock-out zebrafish lines. Zebrafish embryos are clear, which allows researchers to watch the fertilized eggs grow into fully formed baby fish under a microscope. Their transparency also enables the visualization of fluorescently-labeled tissues or cells in transgenic zebrafish embryos. Moreover, zebrafish embryos are permeable to many chemicals and drugs, making them ideal for screening large numbers of toxicology samples or drug candidates.

What are some examples of human diseases that have been successfully modeled in zebrafish? The generation of a knock-out of the dystrophin gene in zebrafish has been shown to closely resemble the severity and progression of Duchenne muscular dystrophy (DMD). Patients with DMD have been found to carry mutations in dystrophin and demonstrate childhood muscle weakness that gets progressively worse with age. In both humans and the zebrafish model, the loss of dystrophin gradually leads to necrotic muscle fibers that are replaced by inflammatory cells, fibrosis, and abnormally-sized muscle fibers (Berget et al. (2012). Dis. Model Mech.). Melanoma has also been successfully modeled in zebrafish. The most commonly identified mutation in human melanomas—a single amino acid change in the gene BRAF—was created in a knock-in zebrafish model. Since cancers are caused by a combination of several genetic alterations, this knock-in zebrafish line was used to screen other potential cancer-causing mutations. When another commonly observed melanoma mutation of the gene SETDB1 was added to the BRAF knock-in zebrafish, a melanoma rapidly developed. These results helped to establish that SETDB1 is an important gene in melanoma growth (Ceol et al. (2011). Nature).

These examples of how humans and zebrafish can manifest the same disease despite our apparent differences makes it is easy to understand why zebrafish are becoming a well-accepted animal model. Although no animal can perfectly model a human disease, these little swimmers have great potential for advancing medical research in the future.